REMARKS

I. STATUS OF THE CLAIMS.

Claims 33, 35, 37-41, 52-57, 59, 68, and 70-76 are presently pending. Claims 1-32, 34, 36, 42-51, 58, 60-67, 69, and 77-78 have been canceled with entry of this amendment without prejudice to subsequent renewal, including in a divisional, continuation, or continuation-in-part. Claims 33, 35, 37-41, 52, 57, 59, 68, and 70-76 have been amended. New claims 79-97 have been added. Support for the amendments to pending claims and the new claims is provided throughout the specification. No new matter has been added.

Independent claim 33 has been amended to specify more particularly a monocyte-derived dendritic cell that substantially lacks CD14 surface marker expression. Support for this amendment is provided throughout the specification, including at, *e.g.*, p. 53, lines 30-31 and p. 55, lines 22-25. Claim 34 has been canceled without prejudice, since its limitations have been incorporated into claim 33. Claims 35 and 37-41, which are dependent on claim 33, have been amended for consistency with claim 33. Claims 35 and 37 have been amended to correct the dependency.

Independent claim 52 has been amended to specify more particularly that the dendritic cells substantially lack expression of CD1a and CD14 surface markers. Claim 57 has been added to specify the at least one antigen comprises a tumor antigen, bacterial antigen, parasite antigen, viral antigen, or autoantigen. Support for this amendment is provided throughout the specification, including at, *e.g.*, p. 4, lines 25-28; p. 9, lines 6-7, p. 13, line 26 to p. 15, line 10; p. 15, lines 26-37; and p. 38, lines 14-30.

Independent claim 68 has been amended to recite more specifically a monocyte-derived dendritic cell that does not substantially express CD1a and CD14 surface markers which comprises one or more of the following characteristics: substantially lacks IL-12 production, exhibits increased IL-10 production, and promotes increased differentiation of T cells to Th0 and/or Th2 cells, as compared to a conventional dendritic cell. Independent claim 72 has been amended to specify the dendritic cells do not substantially express CD1a and CD14 surface markers. Support for these amendments is provided throughout the specification, including at, *e.g.*, p. 55, lines 22-33.

Independent claim 70 has been amended to specify that the monocyte-derived dendritic cells express substantially less CD1a surface marker than conventional dendritic cells, substantially lack expression of CD14 surface marker, and have a cytokine profile that differs from

the cytokine profile of dendritic cells produced by culturing a population of monocyte cells in IL-4, GM-CSF, and a culture medium comprising RPMI. Support for this amendment is provided throughout the specification, including at, *e.g.*, p. 55, lines 22-33. Claim 71, which depends on claim 70, has been amended to specify the cells comprise two or more of the characteristics.

Independent claim 73 has been amended to recite a composition comprising at least one dendritic cell, wherein said at least one dendritic cell does not substantially express CD1a and CD14 and comprises one or more of the following characteristics: produces substantially less interleukin-12 (IL-12), produces substantially more IL-10, and induces or promotes increased T cell differentiation to Th0 or Th2 subtype, as compared to a conventional dendritic cell. Support for this amendment is provided throughout the specification, including at, *e.g.*, p. 55, lines 22-33. Claims 74-76, which depend from claim 73, have been amended for consistency with claim 73.

Claims 59 and 75 has been amended to specify the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. Support for these amendments is provided throughout the specification, including at, *e.g.*, p. 44, lines 33-36.

New dependent claims 79, 81, 83, 84, and 86 specify the dendritic cell expresses CD83 surface marker. Support for these claims is provided throughout the specification, including at, *e.g.*, p. 57, lines 21-24.

New dependent claims 80, 82, and 85 specify the dendritic cell expresses at least one surface marker selected from the group of CD11c, CD13, and CD33 in an amount comparable to that produced by a conventional dendritic cell. Support for these claims is provided throughout the specification, including, at, *e.g.*, p. 55, lines 10-22 and Figure 2.

New dependent claim 87 specifies the dendritic cell induces production of interleukin-6 or interleukin-8 in an amount comparable to that produced by a conventional dendritic cell. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 56, lines 15-16 and Figure 3.

New independent claim 88 is directed to an isolated or purified population of monocyte-derived dendritic cells that express substantially less CD1a surface marker than a conventional dendritic cell and are substantially devoid of expression of CD14 surface marker. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 55, lines 23-33 and p. 24, lines 13-34. New dependent claims 89, 91, and 92, each of which depends from claim 88, specifies the monocyte-derived dendritic cells express one or more of CD11c, CD33, and CD13

surface markers in an amount comparable to that expressed by a conventional dendritic cell. Support is provided throughout the specification, including at, *e.g.*, p. 55, lines 10-22 and Figure 2.

New dependent claim 90, which depends from claim 88, specifies the monocyte-derived dendritic cells substantially express CD83 surface marker. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 57, lines 21-24.

New dependent claim 93, which depends from claim 89, specifies the monocyte-derived dendritic cells do not substantially express CD1a and CD14 surface markers and substantially express $CD11c^+$, $CD13^+$, and $CD33^+$ surface markers. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 55, lines 10-22. New dependent claim 94, which depends from claim 93, specifies the monocyte-derived dendritic cells do not substantially express CD1a and CD14, but substantially express $CD11c^+$, $CD13^+$, $CD33^+$, $CD83^+$ markers. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 57, lines 21-24.

New independent claim 95 is directed to an isolated or purified population of monocyte-derived dendritic cells that express substantially less CD1a surface marker than a conventional dendritic cell and substantially express CD83 surface marker. Support for this claim is provided throughout the specification, including at, *e.g.*, p. 57, lines 21-24. New claim 96, which specifies monocyte-derived dendritic cells further expressing at least one of CD11c, CD13, and CD33 and having at least one of the recited characteristics, and claim 97, which specifies a pharmaceutical composition comprising the dendritic cells of claim 95, are also fully supported by the specification.

II. OBJECTION TO THE SPECIFICATION AND AMENDMENTS TO THE SPECIFICATION.

The specification was objected to because it allegedly contains an embedded hyperlink and/or other form of browser-executable code at page 32, line 33. This objection is traversed in part and overcome in part. Applicants do not intend that this web address be an active link in any related published patent or published application. Thus, this link can be disabled by the Office when preparing the text to be loaded onto the USPTO web database. As indicated in MPEP § 608.01, where Applicants do not intend a hyperlink to be an active link (*i.e.*, such that the link becomes a live web link in the published patent or published application when placed on the USPTO web page), the Examiner should not object to the hyperlink and the hyperlink need not be deleted from the specification because the Office can disable the hyperlink when preparing the text to be

loaded onto the USPTO web page. Nevertheless, in an effort to expedite prosecution, Applicants have amended the specification to remove this web address. Withdrawal of the rejection is respectfully requested.

III. REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH.

Claims 57, 70, and 71 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, the Examiner finds the term "a target cell of an autoimmune response" in claim 57 is indefinite because the term is not defined in the specification and thus the metes and bounds of which cells would be encompassed by the claim cannot be determined. Office Action, p. 3. This rejection is traversed in part and overcome in part.

The meaning of the term "a target cell of an autoimmune response" in claim 57 is clear and unambiguous and would be plainly understood by one of ordinary skill in the art given the state of the art at the time and the teachings of the specification. However, in an effort to expedite prosecution, claim 57 has been amended to indicate that the at least one antigen comprises a tumor antigen, bacterial antigen, parasite antigen, viral antigen, or autoantigen. Support for this amendment is provided throughout the specification, including at, *e.g.*, p. 4, lines 25-28; p. 9, lines 6-7, p. 13, line 26 to p. 15, line 10; p. 15, lines 26-37; and p. 38, lines 14-30.

The Examiner also finds that the phrase "altered cytokine profile" in claim 70 is vague and indefinite because this phrase is not defined in the specification and thus "the metes and bounds of precisely which cells would be encompassed by the claim cannot be determined." Office Action, p. 3. This rejection is traversed in part and overcome in part.

The meaning of the phrase "altered cytokine profile" in claim 70 is clear and unambiguous and would have been plainly understood by a skilled artisan based upon the teachings of the specification and the state of the art at the time the application was filed. Figure 3 of the specification, for example, shows a series of bar graphs depicting cytokine profiles of mDC1 and mDC2. *See, e.g.*, Figure 3 and p. 5, lines 37-38 of the specification. Furthermore, the phrase would have been readily comprehended by one of skill in the art at the time of filing, as is evidenced by the following references. *See, e.g.*, Horton *et al.*, IL-2 plasmid therapy of murine ovarian carcinoma inhibits the growth of tumor ascites and alters its cytokine profile," *J. Immunol.* 1999, 163: 6378-6385 (1999); Arena *et al.*, "Altered cytokine production after human herpes virus type 6 infection,"

New Microbiol. 22(4):293-300 (1999); Van de Vliet *et al.*, "Effects of alpha-galactosylceramide (KRN7000), interleukin-12 and interleukin-7 on phenotype and cytokine profile of human Valpha24+ Vbeta11+ T cells," *Immunology* 98(4):557-63 (1999).

Nevertheless, although Applicants traverse this rejection, in an effort to further prosecution, Applicants have amended claim 70 to recite that the monocyte-derived dendritic cells have a cytokine profile that differs from the cytokine profile of dendritic cells produced by culturing a population of monocyte cells in IL-4, GM-CSF, and a culture medium comprising RPMI.

For at least these reasons, withdrawal of the rejection is respectfully requested.

IV. REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH.

Claim 57 was rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Office Action, p. 3. Specifically, the Examiner finds there is insufficient written description to show that Applicants were in possession of "a target cell of an autoimmune response." This rejection is respectfully traversed in part and overcome in part.

Applicants respectfully traverse the rejection, since a definition of "target cell" is provided in the specification at p. 9, lines 20-23. Nevertheless, this rejection has been overcome by the amendment to claim 57. As amended, claim 57 specifies the at least one antigen comprises a tumor antigen, bacterial antigen, parasite antigen, viral antigen, or autoantigen. As discussed above, support for this amendment is provided throughout the specification.

Claims 58, 59, 68, and 70-76 were under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. Office Action, p. 4. Specifically, the Examiner takes the position that "the specification provides insufficient evidence that the claimed vaccine could function for its intended purpose for the treatment or prevention of essentially all known pathogen-induced diseases, as well as cancers and autoimmune diseases." *Id.* The Examiner is of the opinion that undue experimentation would be required to practice the invention as claimed. Furthermore, the Examiner states that "whereas the specification discloses the details of a number of routine tasks it only vaguely discloses the use of the vaccine of the instant claims." *Id.* The rejection of claim 58 has

been mooted by cancellation of that claim without prejudice to subsequent renewal. The rejection of claims 59, 68, and 70-72 is respectfully traversed as follows.

The term "vaccine" is not included in any of claims 59, 68, and 70-72 and thus the rejection does not properly apply to these claims. In the event the rejection is intended to apply to these claims, which Applicants do not concede, Applicants also traverse the rejection for at least the reasons outlined below.

Section 112, first paragraph, imposes two basic enablement requirements. An applicant for a patent must adequately disclose to those of ordinary skill in the pertinent art, in light of what is known in the art, how to make the claimed invention and how to use the claimed invention throughout its scope without undue experimentation. Whether a disclosure is sufficient to enable one of ordinary skill in the art to practice the claimed invention throughout its scope without having to engage in undue experimentation may be assessed by weighing a variety of factors. In *In re Wands*, 858 F.2d 731, 737, 8 UPSQ2d 1400, 1404 (Bd. Pat. App. & Int. 1986), the Board of Patent Appeals and Interferences outlined the following factors for consideration: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance; (3) the presence of absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Based on a review of these factors set forth in *In re Wands*, Applicants submit the disclosure of the present application clearly provides reasonable guidance to one skilled in the pertinent art to practice the full scope of the claimed invention as set forth in any of claims 59, 68, and 70-76 without undue experimentation. Claim 59, which depends from claim 52, simply specifies that the composition is a pharmaceutical composition and the carrier is a pharmaceutically acceptable carrier. Independent claim 68 specifies a monocyte-derived dendritic cell that does not substantially express CD1a and CD14 surface markers and comprises one or more of the following characteristics: substantially lacks IL-12 production, exhibits increased IL-10 production, and promotes increased differentiation of T cells to Th0 and/or Th2 cells, as compared to a conventional dendritic cell. Independent claim 70 specifies a population of monocyte-derived dendritic cells produced by culturing a population of monocyte cells in interleukin-4 (IL-4), granulocyte macrophage colony stimulating factor (GM-CSF), and a culture medium comprising insulin, transferrin, linoleic acid, oleic acid, and palmitic acid, the monocyte-derived dendritic cells

expressing substantially less CD1a surface marker than conventional dendritic cells, substantially lacking expression of CD14 surface marker and having a cytokine profile that differs from the cytokine profile of dendritic cells produced by culturing a population of monocyte cells in IL-4, GM-CSF, and a culture medium comprising RPMI.

Independent claim 72 presently recites a population of dendritic cells produced by culturing a population of peripheral blood or bone marrow mononuclear cells in interleukin-4 (IL-4), granulocyte macrophage colony stimulating factor (GM-CSF), and Yssel's culture medium, wherein said dendritic cells do not substantially express CD1a and CD14 surface markers and exhibit one or more of the following characteristics: substantially lack interleukin-12 (IL-12) production, induce or promote increased T cell differentiation to Th0 or Th2 subtype, and exhibit substantially increased IL-10 production, as compared to dendritic cells produced by culturing a population of monocyte cells in IL-4, GM-CSF, and a culture medium comprising RPMI.

Independent claim 73 presently recites a composition comprising at least one dendritic cell, wherein said at least one dendritic cell does not substantially express CD1a and CD14 surface markers and comprises one or more of the following characteristics: produces substantially less interleukin-12 (IL-12), produces substantially more IL-10, and induces or promotes increased T cell differentiation to Th0 or Th2 subtype, as compared to a conventional dendritic cell.

The claimed dendritic cells and population of dendritic cells -- as set forth in claims 68 and 70-72, respectively -- and the claimed compositions -- as set forth in claims 59 and 73-76 -- are explicitly defined. The breadth of each claim is particularly circumscribed. Furthermore, the guidance provided by the specification is entirely sufficient and adequate to make and use these cells and compositions. In addition, seven detailed working examples are provided for making the claimed cells and compositions thereof. Moreover, the level of skill of one skilled in the pertinent art at the time of filing the application was at least relatively high as indicated by the fact therapies using dendritic cells to treat an assortment of conditions were generally known and employed.

Regarding claims 58 and 73-76, the Examiner noted these claims formerly recited the term "vaccine" and asserted the specification only "vaguely discloses the use of the vaccine of the instant claims" and "only vaguely discloses highly complex methods such as in vivo treatment of prevention of highly diverse diseases/conditions, which would be expected to be unpredictable." Office Action, p. 4. However, contrary to these assertions, at the time the application was filed, conventional dendritic cell-based immunotherapies were in wide use in a variety of clinical trials and

animals studies and commonly employed in a range of *in vivo* therapeutic approaches as vaccines against a number of diseases, including cancers and viral diseases. *See, e.g.*, Liu *et al.*, "T-Cell Vaccination Alters the Course of Murine Herpesvirus 68 Infection and the Establishment of Viral Latency in Mice," *J. Virology* 73:9849-57 (1999); Berlyn *et al.*, "Developing dendritic cell polynucleotide vaccination for prostate cancer immunotherapy," *J Biotechnol.* 73(2-3):155-79 (1999); Eggert *et al.*, "Biodistribution and Vaccine Efficiency of Murine Dendritic Cells Are Dependent on the Route of Administration," *Cancer Research* 59:3340-3345 (1999); Tjoa et al., "Follow-up evaluation of a phase II prostate cancer vaccine trial," *Prostate* 40(2):125-9 (1999); Onsanto, Vaccine Trials for the Clinician: Prospects for Tumor Antigens," *Oncologist* 2(5):284-299 (1997). See also the specification, including at, *e.g.*, p.46, line 16 to p. 47, line 15. Parallel strategies for using the specific cells and compositions of the invention could be readily developed by one skilled in the art. See the specification, including at, *e.g.*, p. 41, line 8 to p. 49, line 36.

The Examiner states that compositions for *in vivo* use require *in vivo* enablement or a reasonable correlate for its intended use. Office Action, p. 5. The Examiner contends the specification discloses only the induction of mixed lymphocyte reaction *in vitro* and that such disclosure cannot be considered to be a reasonable correlate for demonstrating *in vivo* efficacy. The Examiner further contends that "[a]bsent any specific guidance, i.e., working examples of, *in vivo* use, the instant invention would be highly unpredictable and requiring of undue experimentation to practice as claimed." *Id.* These contentions are misplaced. The specification provides a clear description as to how to make and used the claimed cells and compositions in, for example, *in vivo* and *ex vivo* applications. See the specification, including at, *e.g.*, at p. 41, line 7 to p. 49, line 36. Immunotherapeutic methodologies and regimens using the cells and compositions of the invention are also explicitly described. *Id.* Moreover, as noted in the specification, *in vivo* and *ex vivo* conventional dendritic cell-based therapies were widely used at the time of filing. *See, e.g.*, p. 46, line 14 to p. 49, line 36. Applicants have demonstrated not only mixed lymphocyte responses, but a variety of additional functional properties of their novel dendritic cells, including specific cytokine production and T cell differentiation. As with conventional dendritic cells, one of skill would consider the in vitro studies of the functional properties of the novel dendritic cells of the invention to be reasonably predictive of functional properties of these cells in *in vivo* or *ex vivo* applications.

Based upon the functional properties and phenotypic characteristics of the novel dendritic cells of the invention and known methodologies employing conventional dendritic cells,

Applicants' specification provides enablement and a reasonable correlate for the intended use of the novel dendritic cells and compositions thereof, including in *in vivo* and *ex vivo* applications. Use of the claimed cells or compositions thereof would not be highly unpredictable or require undue experimentation. On the contrary, given the detailed teachings of the specification and the prior art, the specifically defined nature of the invention, the working examples, the state of the art and the likely high level of ordinary skill of one in the art at the time the application was filed, one of ordinary skill in the art to which this application pertains would have been reasonably able to make and use Applicants' particularly claimed dendritic cells and compositions thereof. No undue experimentation would have been required to practice any claim, since each claim is carefully circumscribed. Even if some experimentation would have been necessary to carry out the claimed methods, such experimentation would clearly not support an enablement rejection of the claims. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir., 1984). It has long been established that enablement is not precluded even if some experimentation is required, provided the amount of experimentation is not "unduly extensive." *Atlas Powder Co.*, 750 F.2d at 1576.

The Examiner appears to base the enablement rejection, at least in part, on an allegedly contradictory disclosure. Office Action, p. 4. The Examiner notes that mDC2s of the invention promote a Th0/Th2 response and deter a Th1 response, but that a Th1 response is critical for the treatment of viral infections and cancers. The Examiner further finds the specification discloses (at pp. 48-49) that one of ordinary skill can readily design a specific vaccination method and strategy for a particular disease or disorder based upon strategies used with conventional mDC1. The Examiner finds it unclear as to how one of skill could design a specific vaccination method and strategy for a particular disease or disorder using the novel dendritic cells of the invention based upon strategies used with conventional mDC1s, because conventional mDC1s induce a Th1 response and mDC2s of the invention induce a Th2 response. *Id.* at pp. 4-5. The Examiner also appears to find contradictory the disclosure in the specification at page 49 that mDC2s of the invention claims can be used as adjuvants and Applicants' citation of FUNDAMENTAL IMMUNOLOGY (Paul ed., 1999). The Examiner asserts that this reference describes mDC1s, which are high producers of IL-12, and thus the use of the mDC2s of the instant invention would be highly unpredictable and requiring of undue experimentation to practice as claimed. *Id.* at p. 5.

Applicants respectfully submit the Examiner's rational misses the point. Dendritic cells of the invention do not induce *only* Th0 or Th2 production, with no Th1 production. Rather, the dendritic cells of the invention promote increased of Th0 and/or Th2 and decreased production of Th1. Conventional dendritic cells do not induce only a Th1 with no Th2 or Th0. Conventional DCs promote a Th1 response over a Th2/Th0 response. The fact that the novel dendritic cells of the invention shift the cytokine profile, for example, to Th0 and/or Th2 rather than Th1, as compared to conventional dendritic cells, does not mean that undue experimentation would be required for one of skill in the art to determine how to make or use the claimed cells. Moreover, shifting the balance of this response does not mean that known strategies and methods utilizing conventional DCs are wholly inapplicable to the claimed dendritic cells of the invention or render the use of the claimed dendritic cells entirely unpredictable.

Finally, claim 68 was rejected under § 112, first paragraph, because the claim recites a dendritic cell that promotes differentiation of T cells into Th1 cells and the specification discloses that the dendritic cells of the invention promote the differentiation of T cell into Th2 cells. Applicants thank the Examiner for noting this inadvertent typographical error. This rejection has been overcome by amending claim 68 to properly recite "Th2" cells. Support for this amendment is provided throughout the specification, as is noted by the Examiner.

In summary, the rationale for the enablement rejection does not apply to the pending claims and, in any event, is based on the Examiner's erroneous assertions regarding the technical challenges associated with developing vaccines using dendritic cells of the invention. In particular, the Examiner has failed to appreciate that Applicants have clearly described how to make and use the claimed dendritic cells and compositions thereof. As discussed above, the Examiner's justifications for the enablement rejection do not withstand scrutiny in light of the detailed direction provided in the specification as to how to make and use the claimed dendritic cells and compositions thereof, the well-developed state of the art, the presence of numerous working examples, the explicitly defined claims, and the at least relatively high level of skill of one of ordinary skill in the art at the time of filing. At the time of filing, numerous clinical trials and therapeutic and vaccination strategies had been developed using conventional dendritic cells. One of skill in the art would have readily understood how to adapt such strategies for use with Applicants' novel dendritic cells -- even though such cells have cytokine production profiles that differ from those of conventional dendritic cells. Given the state of the art at the time, the use of the claimed cells and

compositions thereof in immunotherapies, including vaccines, would not be expected to be unpredictable.

For these reasons, Applicants wish to emphasize that the amendments to the pending claims in no way reflect agreement with the Examiner's position or surrender of any subject matter. Rather, Applicants have amended the claims to ensure they accurately reflect Applicants' contribution to the art. Specifically, the preamble of originally filed claims 73-76, for example, recited a "vaccine composition comprising at least one dendritic cell." However, Applicants' contribution relates generally to compositions comprising at least one dendritic cell of the invention and should not be restricted to a particular application. Accordingly, the pending claims have been amended to specify compositions comprising at least one dendritic cell that has the recited properties. In view of the guidance and examples provided in the specification -- in addition to the state of the art at the time of filing, the high level of skill of one of ordinary skill in the art -- Applicants submit the specification clearly enables one skilled in the art to practice the invention as explicitly defined by the claims. For at least these reasons, withdrawal of the rejection is respectfully requested.

V. REJECTIONS UNDER 35 USC § 102(B).

1. EP 0808897 A1

Claims 33-35, 37-41, 52-59, 68, and 70-76 were rejected under 35 USC § 102(b) as allegedly being anticipated by EP 0808897 A1 [hereinafter "the EP '897 application"]. Specifically, the Examiner takes the position that:

> EP 0808897 teaches an antigen presenting cell (APC) identified as being devoid of surface CD1a (see particularly page 3, line 11), i.e., a differentiated APC which expresses substantially less CD1a cell surface marker that [sic] a conventional dendritic cell. Note that the additional limitation of the claims comprise only further characterization of the claimed cell type, e.g., a cell that substantially lacks IL-12 production. These properties are inherent to the cell of the reference. Some claims, e.g., Claim 38, recite product-by-process limitations, e.g., a differentiated cell cultured in Yssel's medium. Absent a showing that the process results in a novel product, said process is irrelevant. Further note that the source of the cells, i.e., monocyte derived, is also irrelevant absent a showing that said source provides novel properties. In the instant case, no such showing has been made. Accordingly, the cells of the references are the cells of the instant claims.

Office Action, p. 6.

The rejection of claims 34 and 58 has been mooted by cancellation of those claims without prejudice. The rejection of claims 33, 35, 37-41, 52-57, 59, 68, and 70-76 is respectfully traversed in part and overcome in part as follows.

To establish a *prima facie* case of anticipation, it must be shown that each and every element as set forth in the claim is disclosed, either expressly or inherently, in the single cited prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *In re Cruciferous Sprout Litigation*, 64 USPQ2d 1202 (Fed. Cir. 2002). "The identical invention must be shown as in complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Under the principles of inherency, the prior art disclosure need not be express in order to anticipate. A prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Schering Corp. v. Geneva Pharmaceuticals*, 339 F.3d 1373, 67 UPSQ2d 1664 (Fed. Cir. 2003) (citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999). Inherency may not be established by probabilities or possibilities. That a certain thing *may* result from a given set of circumstances is **not** sufficient for a finding of anticipation. *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1365, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999) (emphasis added). For a determination of anticipation to be proper, there must be no genuine dispute that all the limitations of the claimed invention are disclosed, either expressly or inherently, by the allegedly anticipating cited prior art reference. *Hazani v. United States ITC*, 126 F.3d 1473, 44 USPQ2d 1358 (Fed. Cir. 1997). "A limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art." *Schering Corp.*, 339 F.3d at 1373, 67 UPSQ2d at 1664. Proof that the missing description is inherent in the single prior art reference is required for a finding of anticipation. *Id.*

Applicants respectfully submit that a *prima facie* case of anticipation has not been established. Specifically, it has not been shown that each and every element of claims 33, 35, 37-41, 52-57, 59, 68, and 70-76 is found -- either explicitly or inherently -- in the EP '897 application. First, each of the claims explicitly specifies dendritic cells that are substantially devoid of expression of CD1a surface marker. The EP '897 application discloses macrophages -- not dendritic cells --

that are substantially devoid of CD1a. The EP '897 application expressly states that macrophages are not dendritic cells. *See, e.g.*, p. 2, lines 38-45.

In addition, it has not been shown the EP '897 application teaches or suggests dendritic cells having one or more of the specified characteristics, such as, *e.g.*, substantially lacking IL-12 production, promoting Th0 and/or Th2 T cell differentiation, or exhibiting increased IL-10 production as compared to conventional dendritic cells. No evidence is provided that any of the missing limitations is necessarily present in the application or necessarily flows from its teachings.

Furthermore, as presently drafted, independent claims 33, 52 and 70 specify dendritic cells that substantially lack expression of CD1a and CD14 surface marker. In contrast, the EP '897 application describes macrophages that are substantially devoid of CD1a, but that express CD14 antigens present on their surface. *See, e.g.*, EP '897 application, p. 3, lines 4-8 and Tables 2 and 4.

Independent claims 68, 72, and 73 presently specify dendritic cells that do not substantially express CD1a and CD14 surface markers. This phenotype of these cells differs distinctly from that of the macrophage disclosed in the EP '897 application. *See, e.g.*, the EP '897 application, p. 3, lines 4-8 and Tables 2 and 4. For at least these reasons, Applicants submit the rejection is improper or nevertheless overcome.

Applicants submit that none of new claims 79-97 is anticipated by the EP '897 application. For example, new claims 79-87 depend from the independent claims discussed above and thus are novel for at least the reasons set forth above. New independent claim 88, which specifies a population of monocyte-derived dendritic cells that express substantially less CD1a surface marker than a conventional dendritic cell and are substantially devoid of expression of CD14 surface marker, is also novel for at least the same reasons discussed above.

New dependent claims 89-94, which depend ultimately from claim 88, and new independent claim 95 (and claims 96-97 dependent thereon) are likewise novel, as they incorporate additional limitations that are not expressly or inherently disclosed in the EP '897 application. For example, new claim 95 specifies an isolated or purified population of monocyte-derived dendritic cells that express substantially less CD1a surface marker than a conventional dendritic cell and substantially express CD83 surface marker. In contrast, the EP '897 application discloses macrophages that are substantially devoid of CD83. *See, e.g.*, p. 3, lines 40-41 and Tables 2 and 4 of the EP '897 application.

2. Ito

Claims 33-35, 37-41, 52-59, 68, and 70-76 were rejected under 35 USC § 102(b) as allegedly being anticipated by Ito *et al.*, *J. Imunol.* 163:1409-19 (1999) [hereinafter "Ito"]. Specifically, the Examiner takes the position that:

> Ito et al. teaches an APC identified as being devoid of surface CD1a (see particularly page 1415, column 2, ***Fraction 3*** and ***Fraction 2***). [A]s set forth above, the additional limitations of the claims comprise only further characterization of the claimed cell type, e.g., a cell that substantially lacks IL-12 production. These properties are inherent to the cell of the reference. Some claims, e.g., Claim 38, recite product-by-process limitations, e.g., a differentiated cell cultured in Yssel's medium. Absent a showing that the process results in a novel product, said process is irrelevant. Further note that the source of the cells, i.e., monocyte derived, is also irrelevant absent a showing that said source provides novel properties. In the instant case, no such showing has been made. Accordingly, the cells of the references are the cells of the instant claims.

Office Action, pp. 6-7 (emphasis in original).

The rejection of claims 34 and 58 has been mooted by cancellation of those claims without prejudice. The rejection of the remaining claims is respectfully traversed as follows.

Under 35 USC § 102(b), a person is entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States." The present application, U.S. Patent Application Serial No. (USSN) 09/760,388, which was filed on January 10, 2001, properly claims priority from provisional USSN 60/175,552, filed January 11, 2000, and USSN 60/181,957, filed February 10, 2000. The specification of the present application makes specific reference to each earlier-filed provisional application to which priority is claim and explicitly provides that the disclosure of each provisional application is incorporated by reference in the present application. Pursuant to 35 USC § 120, the present application is entitled to claim priority from these provisional applications. All of the claims of the present application are fully supported by the earlier-filed provisional application and are thus entitled to a priority filing date of January 11, 2000 or at least February 10, 2000.

Ito was published in August 1999 and thus is not a proper prior art reference under 102(b), since it was not published more than one year before the effective filing date of the instant application. Thus, the 102(b) rejection is improper.

Nevertheless, even if the subject matter relied upon in Ito were to constitute prior art, which Applicants do not admit, the rejection is nevertheless overcome by the Declaration of Juha

Punnonen and Chia-Chun J. Chang Under 37 CFR § 1.131, which is attached hereto. This declaration sets forth facts demonstrating the inventors reduced the claimed invention to practice in the United States prior to the August 1999 publication date of Ito.

For at least these reasons, withdrawal of the rejection of claims 33, 35, 37-41, 52-57, 59, 68 and 70-76 is respectfully requested. Applicants also submit that Ito does not apply to new claims 79-97 for at least the same reasons.

3. Rissoan

Claims 33-35, 37-41, 52-59, 68, and 70-76 were rejected under 35 USC § 102(b) as allegedly being anticipated by Rissoan *et al.*, *Science* 283:1183-86 (Feb. 1999) ["Rissoan"]. Specifically, the Examiner finds that:

> Rissoan et al. teaches an APC identified as substantially lacks [sic] IL-12 production that induce [sic] Th2 differentiation" (see particularly page 1183, column 3, and page 1184, column 3). As set forth above, the additional limitations of the claims comprise only further characterization of the claimed cell type, e.g., being devoid of surface CD1a. These properties are inherent to the cell of the reference. Some claims, e.g., Claim 38, recite product-by-process limitations, e.g., a differentiated cell cultured in Yssel's medium. Absent a showing that the process results in a novel product, said process is irrelevant. Further note that the source of the cells, i.e., monocyte derived, is also irrelevant absent a showing that said source provides novel properties. In the instant case, no such showing has been made. Accordingly, the cells of the references are the cells of the instant claims.

Office Action, p. 7.

The rejection of claims 34 and 58 has been mooted by cancellation of those claims without prejudice. The rejection of the remaining claims is respectfully traversed as follows.

First, Rissoan published on February 19, 1999 and thus is not a proper prior art reference under 102(b), since it was not published more than one year before the effective filing date of the instant application. Thus, the 102(b) rejection is improper.

Furthermore, even if the subject matter relied upon in Rissoan were to constitute prior art, which Applicants do not admit, the rejection is improper. No evidence is provided that any dendritic cell disclosed in Rissoan substantially lacks expression of CD1a surface marker. For a limitation to be inherent in a reference, it must necessarily be present in the reference. The extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the reference.

Nor is any evidence provided which demonstrates that additional limitations of the rejected claims are necessarily present in or flow from the teachings of Rissoan. For example, the lymphoid dendritic cells that Rissoan describes which did not produce significant levels of IL-12 and induced Th2 differentiation (termed "DC2" cells in Rissoan) were derived from plasmacytoid cells -- not monocytes. Rissoan expressly distinguishes DC2 cells from dendritic cells derived from peripheral blood monocytes (termed "DC1" cells). Rissoan states that unlike monocyte-derived DC1 cells, lymphoid DC2 cells do not express myeloid antigens, including, for example, CD11c, CD13, and CD33.

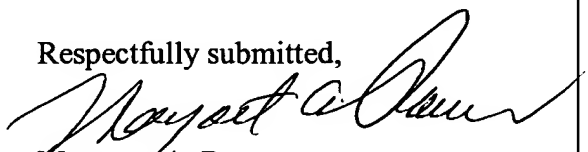
The rejection is nevertheless overcome by the Declaration of Juha Punnonen and Chia-Chun J. Chang Under 37 CFR § 1.131 attached hereto. This declaration sets forth facts demonstrating the inventors reduced the claimed invention to practice in the United States prior to the February 19, 1999 publication date of Rissoan.

For at least these reasons, withdrawal of the rejection of claims 33, 35, 37-41, 52-57, 59, 68 and 70-76 is respectfully requested. Applicants also believe Rissoan does not apply to new claims 79-97 for at least the same reasons.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 298-5809.

Respectfully submitted,



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